REMARKS

Amendments in the claims

Following entry of the amendment requested herein, Claims 28-36, 38-41, 45-48, 52-56 are pending. Of the pending Claims, Claims 38-40, 45-48, 52-56 are withdrawn. Claims 1-27, 37, 42-44, 49-51 and 57-59 were cancelled previously.

Claim 28 is amended herein to recite "the drug-containing adhesive matrix is produced by metering rotigotine free-base into a solvent-free melt at a temperature of between 70°C and 200°C". Support for this amendment can be found, at least, at page 11, lines 1-6 and 18-23. Claim 28 is further amended to enhance clarity of the claimed features.

Claim 30 is amended herein for consistency with the recitation of its independent claim.

No new matter is added, and no change in inventorship is believed to occur, as a result of any amendment herein.

RESPONSE TO OFFICE ACTION DATED 9 DECEMBER 2009

1. Rejection under 35 U.S.C. §103(a) – Ulman in view of Müller

Claims 28-32, 34-36, and 41 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,658,975 ("Ulman") in view of U.S. Patent No. 6,620,429 ("Müller"). The rejection is respectfully traversed.

The alleged combination of these documents fails to meet all the criteria necessary to establish a presumption of *prima facie* obviousness for at least these reasons:

1) the combined documents fail to provide for all of the claimed features;
2) these documents also fail to provide an apparent reason to combine their respective features and further include the missing elements necessary to recreate a hot-melt TTS in the fashion claimed by Applicant;
3) these documents also fail to provide a reasonable expectation of success in modifying aspects of their disclosures as necessary to recreate Applicant's claims.

1.1 The alleged combination of Ulman and Müller does not teach all of Applicant's claimed features.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580

(CCPA 1974). The alleged combination of Ulman and Müller fails to disclose all claimed features including (1) metering rotigotine free-base into a solvent-free melt at a temperature of between 70°C and 200°C, and (2) the adhesive matrix exhibiting at 160°C a dynamic viscosity of not more than 100 Pa·s.

(1) Metering rotigotine free-base into a solvent-free melt at a temperature of between 70°C and 200°C: The Examiner points out that "Ulman differs from the instant application in that it does not disclose the rotigotine in base form… Use of rotigotine… in a transdermal formulation was known in the art… as disclosed by Müller." (Action, p. 5). As indicated in the Office Action, it is clear that Ulman does not disclose a hot-melt composition comprising rotigotine free-base. With respect to the further indication that Müller mentions a transdermal therapeutic system (TTS) containing rotigotine, Applicant submits that the TTS of Müller is essentially different from the claimed hot-melt system. The Examiner's attention is particularly directed to the fact that Müller describes a solvent-based TTS which is manufactured under very different conditions. The Müller system requires conversion of an active substance salt into its free base with an organic solvent whereas the claimed system uses a solvent-free melt of an adhesive matrix. Neither of the cited documents provides teaching or suggestion that Müller can be modified to become a solvent-free system.

Furthermore, no cited document teaches or suggests that rotigotine is compatible with a hot-melt system; in other words, no cited publication teaches the claimed feature, metering rotigotine free-base into a solvent free melt of an adhesive matrix at a temperature of between 70°C and 200°C. Rotigotine was believed to be unstable under hot-melt conditions at the time of filing, because its relatively low melting point (75°C) leads to phase separation and susceptible to oxidation at elevated temperatures. Thus, a person having ordinary skill would not have employed a hot-melt system due to the expected decomposition that would result in loss of bioactivity and produce undesired side-products/impurities which are not acceptable in a pharmaceutical product. This feature is neither taught nor suggested in any of the cited documents.

(2) Adhesive matrix exhibiting at 160°C a dynamic viscosity of not more than 100 Pa·s: The Examiner also points out that "[t]he Ulman reference does not address the viscosity of instant claim 18 [*sic*]… Properties are the same when the structure and composition are the

same." (Action, p. 4, emphasis added). As discussed above, Ulman does not teach a hot-melt composition comprising rotigotine free-base and Müller teaches a substantially different TTS system. Given that Müller requires preparation of rotigotine free-base using an organic solvent, a combined teaching would necessarily include a solvent-based system unless there is prior art teaching or suggestion that the Müller system can be modified to a solvent-free TTS. The claimed TTS, which is structurally different from the alleged combination, is expected to have different properties as indicated by the Examiner.

As illustrated above, the alleged combination of Ulman and Müller fails to provide for all of the claimed features, and therefore a presumption of *prima facie* obviousness has not been established.

1.2 Ulman and Müller fail to provide an apparent reason to combine their respective features

Ulman and Müller are not combinable because of (1) incompatibility of hydrophilic TTS with hydrophobic drug, and (2) no reason to reconcile the mismatched aspects of Ulman and Müller.

(1) Incompatibility of hydrophilic TTS with hydrophobic drug: Applicant respectfully submits that improvement in TTS described by Ulman is mischaracterized in the present Office Action. Unlike the Examiner's indication that the amount of any drug can be increased or controlled, Ulman describes that the amount of only hydrophilic drugs can be increased or controlled as follows:

- "One advantage is that higher dosages of hydrophilic drugs can be employed without destroying the pressure sensitive adhesive" (Ulman, col. 1, lines 65-66, emphasis added).
- "The hot-melt silicone pressure sensitive adhesive compositions of the instant invention have improved hydrophilic characteristics while retaining adhesion, shear and release" (Ulman, col. 2, lines 14-17, emphasis added).
- "Due to the presence of the siloxylated polyether waxes in the hot-melt silicone pressure sensitive adhesive composition of the instant invention, the resulting adhesives have improved hydrophilic characteristics, thus allowing quicker delivery of drugs that are hydrophilic in nature" (Ulman, col. 7, lines 37-41, emphasis added).

Ulman does not describe or suggest explicitly or implicitly that such improvement would exist for non-hydrophilic drugs, such as lipophilic drugs. Therefore, a person of ordinary skill would not look to combine a lipophilic drug (*e.g.*, rotigotine free-base) with a hot-melt adhesive expressly designed for improved performance with hydrophilic drugs (Ulman's system).

It should be noted that chemical compatibility between the polymer matrix and the drug is a basic criterion and there was a unique problem with rotigotine:

> In hydrophobic adhesives such as silicones, Rotigotine is soluble in trace amounts only, which is why it must be dispersed. The viscosity of the molten Rotigotine is very low, as a result of which there may be considerable viscosity difference during the process between the adhesive and the active substance. (specification, p. 26, emphasis added)

Thus, use of rotigotine in the Ulman TTS would not have led to an increased amount of rotigotine in the TTS. The Ulman and Müller teachings actually run counter to a finding of obviousness, as one of ordinary skill in the art would be dissuaded from selecting and joining the incompatible features of these teachings. See *In re Grasselli*, 713 F.2d 731, 218 USPQ 769 (Fed. Cir. 1983) (improper to combine references where the references teach away from their combination).

Drug concentration is a critical factor in a TTS system because high level of drug concentration is needed for adequate delivery. However, no method was known to attain this goal when rotigotine is used.

(2) No reason to reconcile the mismatched aspects of Ulman and Müller: MPEP § 2143 states that "[t]he key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious," which should be made explicit, as directed by *KSR Int'l Co. v. Teleflex Inc.* In this case, there is no reason provided in the present rejection as to how or why a person of ordinary skill would or could reconcile the mismatched aspects of Müller and Ulman. See *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) (improper to combine references where the references teach away from their combination). The motivation asserted to use the Ulman composition is "because the amount of drug release from the transdermal formulation can be increased or controlled". (Ulman, col. 1, lines 61-67). This is in direct reference to

hydrophilic compositions for use with hydrophilic drugs. As such, the stated motivation in the present rejection is directly tied to hydrophilic drugs, not lipophilic drugs like rotigotine free-base. Based on this motivation, one of ordinary skill in the art would follow Ulman for improved hydrophilic drug performance and would consider Ulman unfit for use with rotigotine free-base. No reason is given as to how an ordinary skilled artisan would reconcile their disparate teachings.

1.3 No reasonable expectation of success

When formulating a *prima facie* case of obviousness, a reasonable expectation or predictability of success is required, as noted in MPEP § 2143.02 and in *KSR v. Teleflex*, 550 U.S. 398, 82 USPQ2d 1385 (2007): "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art."

There is no basis for such predictability found in Ulman and Müller or provided based on the general knowledge in the art. In particular, there is no guidance provided to make a solvent-free, hot-melt TTS comprising rotigotine free-base, as recited in Claim 1. There are at least two factors supporting that there was no reasonable expectation of success at the time of the invention. First, a solvent-based system described in Müller was not expected to be useful for making the claimed TTS system because the solvent-based system can be charged with a low-level of rotigotine:

> [i]t is not possible in a single-step operation to introduce a Rotigotine charge of more than about 1.5 mg/cm^2 in a silicone TTS produced by the solvent-based method. (specification, p. 9).

Second, rotigotine was believed to be unstable under hot-melt conditions, because its relatively low melting point (75°C) leads to phase separation and susceptibility to oxidation at elevated temperatures. It should be noted that Examples 1 and 2 of Müller describe a step of drying rotigotine at 50°C which is intended to avoid the risk of oxidation. Due to such known properties, therefore, a person having ordinary skill would not have applied a hot-melt technology to a rotigotine-containing TTS.

Surprisingly, it was found that the claimed invention using a solvent-free, hot-melt system produces the following unexpected results. The claimed system achieves a high

rotigotine charge (up to over 40% by weight) which is significantly higher than that of a solvent-based system, as well as more controllable release. Rotigotine, which is present in a solidified melt, is protected from critical environmental factors such as light and oxygen (specification, p. 9, lines 5 & 6), as demonstrated by improved stability against oxidation and presents in resulting matrix at a purity which is routinely better than 98% and generally over 99% (specification, p. 25, lines 2-5). In addition, the claimed TTS enables extended release, inducing an average plasma concentration of 0.4-2 ng/ml rotigotine over a period of at least 5 days (specification, p. 22, last paragraph).

Lastly, as explained in the previous response dated 20 October 2009, the assertion that "[U]lman does not preclude use of lipophilic drugs in the disclosed adhesive composition" does not amount to a reasonable expectation that rotigotine free-base would be successful in the hydrophilic composition of Ulman. This assertion fails to address the present issue – identification of a reason by which one of ordinary skill in the art would in fact select and combine Ulman and Müller. See *In re Kahn*, 441 F3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning to support the legal conclusion of obviousness."). The lack of an express statement prohibiting use of lipophilic drugs in Ulman is not enough to overcome the expressly noted tailoring and function of the Ulman composition for improved performance with hydrophilic drugs; *i.e.*, Ulman's silence does not overcome the expressly stated (and contrary) purpose of Ulman. In any event, there is a strong presumption that the Ulman composition would work only with hydrophilic drugs, as this property is diametrically opposed to favoring hydrophobic substances. Properly viewing the references, without the benefit of the present claims, it is an improper stretch to assert one of ordinary skill in the art would have used the hot-melt composition of Ulman in seeking a suitable vehicle for the lipophilic rotigotine free-base. Although "[t]ransdermal drug delivery is influenced by many factors," there is no reasonable expectation of success in combining the Ulman composition with rotigotine free-base.

Accordingly, Ulman and Müller do not establish a presumption of *prima facie* obviousness as to Claims 28-32, 34-37, and 41. Applicant respectfully requests reconsideration of the claims and withdrawal of the rejection.

2. Rejection under 35 U.S.C. §103(a) – Ulman in view of Müller & Noel

Claims 28 and 33 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,658,975 ("Ulman") in view of U.S. Patent No. 6,620,429 ("Müller"), further in view of U.S. Patent No. RE 36,754 ("Noel"). The rejection is respectfully traversed.

Noel is provided for teaching use of the waxes ozokerite and ceresine to decrease dynamic viscosity of a hot-melt pressure-sensitive adhesive at temperatures up to 200°C (Noel, abstract; col. 5, lines 1 and 12–14). This information does not strengthen the previous rejection against Claim 28 since the claim does not recite any specific waxes. Therefore, Claim 28 is nonobvious at least for the same reason explained above.

Claim 33 is not obvious over Ulman in view of Müller and Noel at least for the same reason that independent Claim 28, from which Claim 33 depends, is nonobvious over the alleged combination. Noel describes in general that drugs may be included in the matrix. However, it fails to teach not only specific drugs, in particular rotigotine, but also the amount of the drug to be incorporated. It should be noted that another important feature of the claimed method is the stability of the drug and the carrier. If the temperature required is too high, the drug may decompose, for example, by oxidation or evaporation. Noel simply fails to address issues regarding such practical applicability of the proposed composition for transdermal administration. Furthermore, it does not teach the rheologic properties and parameters of the active ingredient, such as for example skin tolerance, solubility and release properties, and chemical stability of the active ingredient which all need to be considered in developing a pharmaceutical composition. Lastly, Noel does not disclose that oxidation-sensitive rotigotine is (and remains) chemically stable during matrix manufacturing steps at a temperature of 125°C to 200°C, as shown in the Examples of the present specification. Therefore, Noel is not combinable with the other cited publications for the reasons above.

Ulman, Müller and Noel individually or in combination, even if they are properly combinable, which Applicant does not admit, fail to teach all claim features such as (1) metering rotigotine free-base into a solvent-free melt at a temperature of between 70°C and 200°C, and (2) the adhesive matrix exhibiting at 160°C a dynamic viscosity of not more than

100 Pa·s. Ulman, Müller and Noel are not combinable because of their incompatibility and no teaching to reconcile the mismatched aspects. Lastly, there was no reasonable expectation of success to make the claimed invention based on the cited publications. Therefore, the asserted combination does not establish a presumption of *prima facie* obviousness as to Claims 28 and 33.

Accordingly, Claims 28 and 33 are not obvious over Ulman in view of Müller and further in view of Noel. Withdrawal of the present rejection is respectfully requested.

3. Provisional obviousness-type double patenting

(1) Claims 28-36 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-23 of co-pending U.S. Application Serial No. 10/630,633 ('633).

Applicant respectfully submits that the rejection over U.S.'633 is improper because the present application (filed 29 July 2003 as a PCT application) was filed earlier than U.S.'633 application (filed 6 February 2004). Even if an obviousness-type double patenting issue exists between the applications, which Applicant does not admit, a terminal disclaimer cannot be filed in this application because the patent to be issued from the present application will expire earlier and there is no term to be disclaimed. If necessary, this issue should be addressed in the later-filed application, i.e., U.S.'633. Therefore, withdrawal of the present rejection is respectfully requested.

(2) Claims 28-36 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-36 of copending Application No. 10/139,894 ('894).

Applicant maintains that it is premature to discuss any substantive argument (or terminal disclaimer) to overcome a provisional double patenting rejection at this time. However, Applicant elected to make the following observations in the interest of advancing prosecution. The currently pending claims of U.S.'894 are drawn to a method-of-use invention. More specifically, the U.S.'894 claims relate to a method for treating Parkinson's disease comprising administering rotigotine free-base using a transdermal system where the transdermal system does not employ a hot-melt adhesive. Nonobviousness of applying a hot-

melt adhesive to a rotigotine TTS is fully discussed above, and the present claims are not obvious over the U.S.'894 claims at least for the same reason.

(3) Claims 28-36 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12 of copending Application No. 10/140,096 ('096).

Likewise, it is premature to discuss any substantive argument (or terminal disclaimer) to overcome a provisional double patenting rejection over U.S.'096. However, Applicant elected to make the following observations in the interest of advancing prosecution. The currently pending claims of U.S.'096 are drawn to a method-of-use invention. More specifically, the U.S.'096 claims relate to a method for treating restless leg syndrome (RLS) comprising administering rotigotine where the method does not employ a TTS comprising a hot-melt adhesive. Nonobviousness of applying a hot-melt adhesive to a rotigotine TTS is fully explained above, and the present claims are not obvious over the U.S.'096 claims at least for the same reason.

(4) Claims 28-36 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 10/139,864 ('864).

Again, it is premature to discuss any substantive argument (or terminal disclaimer) to overcome a provisional double patenting rejection over U.S.'864. However, Applicant elected to make the following observations in the interest of advancing prosecution. The currently pending claims of U.S.'864 are drawn to a transdermal delivery system comprising a self-adhesive matrix containing a self-adhesive polymer and microreservoirs; that is, the claimed subject matter does not relate to a hot-melt adhesive. Nonobviousness of applying a hot-melt adhesive to a rotigotine TTS is fully explained above, and the present claims are not obvious over the U.S.'864 claims at least for the same reason.

(5) Claims 28-36 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-120 of copending Application No. 11/239,701 ('701).

Likewise, it is premature to discuss any substantive argument (or terminal disclaimer) to overcome a provisional double patenting rejection over U.S.'701. However, Applicant

elected to make the following observations in the interest of advancing prosecution. The currently pending claims of U.S.'701 are drawn to a method-of-use invention. More specifically, the U.S.'701 claims relate to a method for treating a disease associate with the dopaminergic system comprising administering rotigotine using a patch where the patch does not employ a hot-melt adhesive. Nonobviousness of applying a hot-melt adhesive to a rotigotine TTS is fully explained above, and the present claims are not obvious over U.S.'701 claims at least for the same reason.

The rejection over U.S.'894, U.S.'096, U.S.'864 and U.S.'701 is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the co-pending application issues as a patent. Withdrawal of the present rejection is respectfully requested.

(6) Claims 28-36 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-110 of copending Application No. 11/239,772 ('772). U.S.'722 application was abandoned per Notice of Abandonment dated 22 July 2009, and accordingly the rejection over U.S.'722 application is rendered moot.

4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.